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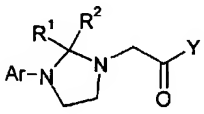

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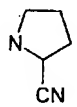

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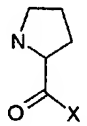

(3)

(57) Abstract: Compounds according to general formula (1) are new. They are readily prepared by the reaction of an N-aryl imidazolidine with an acetic acid derivative, and are useful in the synthesis of pharmaceutically active ethylenediamine derivatives. In this general formula, Ar is an aryl group selected from optionally substituted phenyl and optionally substituted heteroaryl groups. The groups R?1¿ and R?2¿ may be the same or different, and each is selected from H and alkyl groups. Preferably they are selected from H, methyl and ethyl. More preferably they are both H, both methyl, or one is H and the other is methyl. The group Y is selected from OH, O-alkyl, O-aralkyl, 2-cyano-1-pyrrolidyl (2) and a group according to general formula (3). The group X is selected from OH, O-alkyl, O-aralkyl, O-resin, NH¿2?, NH-alkyl, NH-aralkyl, and NH-resin.

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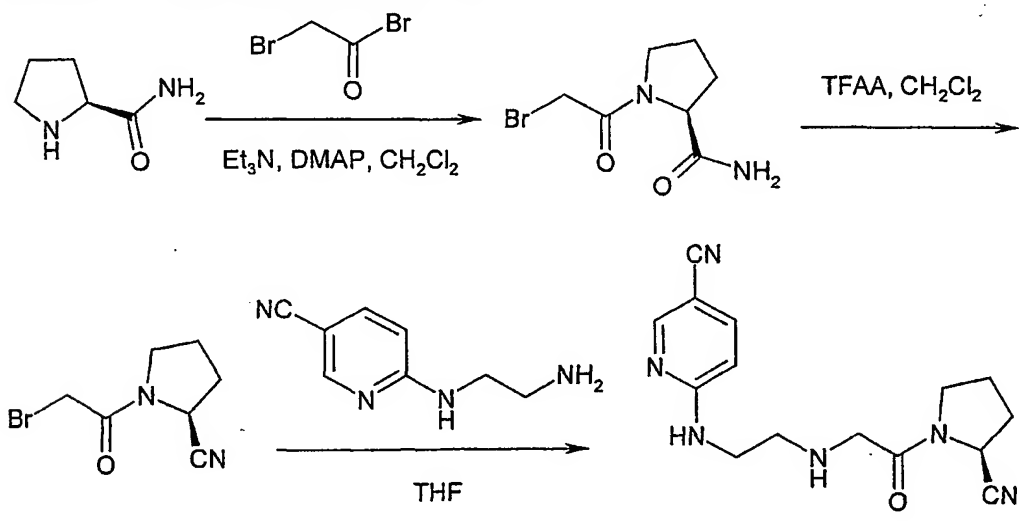
IMIDAZOLIDINEACETIC ACID DERIVATIVES

The present invention relates to imidazolidineacetic acid derivatives, to a process for the synthesis thereof, and to the use of these compounds in the preparation of pharmaceutically important ethylenediamine derivatives.

BACKGROUND

International Patent Application PCT/EP97/06125 (published as WO98/19998; equivalent to EP 0 937 040 and US 6,011,155) discloses, *inter alia*, a series of *N*-(aminoethyl)glycine derivatives that are inhibitors of dipeptidyl peptidase IV (DP-IV, CD26, EC.3.4.14.5). One of these (NVP-DPP728) is currently in clinical trials for the treatment of type 2 diabetes. The synthesis of NVP-DPP728 as described in the patent application is shown in Scheme 1.

Scheme 1 – Preparation of NVP-DPP728



NVP-DPP728

The key step is the reaction of the *N*-substituted ethylenediamine with (2*S*)-1-(2-bromoacetyl)pyrrolidine-2-carbonitrile. There are problems with this step due to non-selective reaction of the nucleophilic amine groups present in the substrate and in the product with the bromide. This leads to the formation of several side products which are

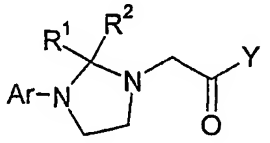
difficult to separate from the desired product and hence to an unacceptably low yield. Therefore, considering the importance of this series of compounds as potential drug therapies for type 2 diabetes, there exists a need for a synthetic route that is selective, higher yielding and amenable to scale-up.

SUMMARY OF THE INVENTION

We have found that the synthesis of *N*-(aminoethyl)glycine derivatives such as NVP-DPP728 is improved by using an imidazolidine derivative rather than an ethylenediamine derivative as the nucleophilic component in the alkylation step. The product of this modified alkylation step is a substituted imidazolidineacetic acid. In a first aspect, the present invention comprises these novel imidazolidineacetic acid derivatives. In a second aspect, the present invention comprises the use of the compounds for the preparation of pharmaceutically active agents, and particularly *N*-(aminoethyl)glycine derivatives. In further aspects the present invention comprises a process for the synthesis of these compounds wherein a 1-arylimidazolidine derivative is reacted with a haloacetyl or analogous species, and novel 1-arylimidazolidine derivatives that are useful as starting materials for the preparation of the compounds.

DETAILED DESCRIPTION OF THE INVENTION

In a first aspect, the present invention comprises a series of novel imidazolidineacetic acid derivatives according to general formula **1**.

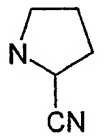


1

In this general formula, Ar is an aryl group selected from optionally substituted phenyl and optionally substituted heteroaryl groups. The optional substituents are selected from alkyl groups, acyl groups, OH, O-alkyl, O-acyl, NH_2, NH-alkyl, $N(alkyl)_2$, NH-acyl, N(alkyl)-acyl, $N(acyl)_2$, F, Cl, Br, I, CF_3, NO_2, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN. The aryl group may have up to three such substituents which may be the same or different.

The groups R^1 and R^2 may be the same or different, and each is selected from H and alkyl groups. Preferably they are selected from H, methyl and ethyl. More preferably they are both H, both methyl, or one is H and the other is methyl.

The group Y is selected from OH, O-alkyl, O-aralkyl, 2-cyano-1-pyrrolidyl (**2**) and a group according to general formula **3**.



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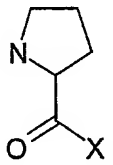


3

The group X is selected from OH, O-alkyl, O-aralkyl, O-resin, NH_2, NH-alkyl, NH-aralkyl, and NH-resin.

Compounds according to general formula **1** in which Y is 2-cyanopyrrolidyl or a group according to general formula **3** have a stereogenic centre ("asymmetric carbon atom") and so can exist as optical isomers. The scope of the present invention includes all such isomers, whether they are in the form of single enantiomers or mixtures of enantiomers (including racemates).

As used herein, the term "heteroaryl" denotes a five- or six-membered aromatic ring with between one and three heteroatoms selected from oxygen, nitrogen and sulphur. Examples of heteroaryl groups include furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridyl, pyrimidyl, triazinyl and the like. Oxo tautomers of hydroxy-substituted heteroaryl groups, such as pyridone and pyrone are also considered to be heteroaryl groups.

As used herein, the term "alkyl" denotes linear, branched and cyclic saturated hydrocarbon groups with up to eight carbon atoms. Examples of alkyl groups include methyl, ethyl, isopropyl, cyclobutyl, neopentyl, cyclobutylethyl and the like.

As used herein, the term "acyl" denotes a group RC(=O), where R is hydrogen or a linear, branched or cyclic saturated or unsaturated hydrocarbon group with up to eight carbon

atoms. Examples of acyl groups include formyl, acetyl, cyclohexylcarbonyl, benzoyl, phenylacetyl and the like.

As used herein, the term "aralkyl" denotes an alkyl group substituted with one or more phenyl or heteroaryl groups. Examples of aralkyl groups include benzyl, phenethyl, trityl, fluorenylmethyl and the like.

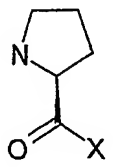
As used herein, the term "resin", when used as a chemical entity such as in O-resin and NH-resin, denotes any of the polymeric resins used for solid-phase synthesis of organic molecules.

In a preferred embodiment, the group Ar is selected from optionally substituted phenyl and optionally substituted pyridyl. More preferably, it is optionally substituted pyridyl. More preferably still, it is optionally substituted 2-pyridyl. Yet more preferably it is 5-monosubstituted 2-pyridyl. Most preferably it is 5-cyano-2-pyridyl.

In another preferred embodiment, the group Y is selected from OH, O-alkyl and O-aralkyl.

In another preferred embodiment Y is 2-cyano-1-pyrrolidyl, and more preferably it is (2*S*)-2-cyano-1-pyrrolidyl.

In another preferred embodiment Y is a group according to general formula **3**. More preferably, Y is a group according to general formula **3** and X is selected from OH, O-alkyl, O-aralkyl, NH_2, NH-alkyl and NH-aralkyl. In another more preferred embodiment X is O-resin or NH-resin. In another more preferred embodiment Y is a group according to general formula **3** in which the absolute configuration is 2*S* as shown in general formula **3**^{A}.



3^{A}

Individual preferred compounds within the present invention include:

N-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-proline;

N-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-proline methyl ester;

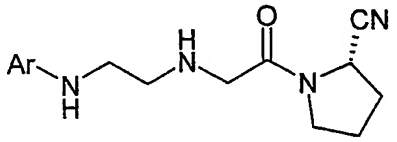
N-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-proline benzyl ester;

N-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-proline *tert*-butyl ester;

N-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-prolineamide; and

(2*S*)-1-(2′-(3″-(5‴-cyano-2‴-pyridyl)imidazolidine)acetyl)pyrrolidine-2-carbonitrile.

Compounds according to general formula **1** are useful for the preparation of pharmaceutically active agents, and this use is a second aspect of the present invention. In particular, the compounds are useful as intermediates in the synthesis of compounds according to general formula **4** disclosed in WO98/19998. These compounds are inhibitors of dipeptidyl peptidase IV and are considered to have potential as agents for the treatment of, *inter alia*, type 2 diabetes and impaired glucose tolerance.



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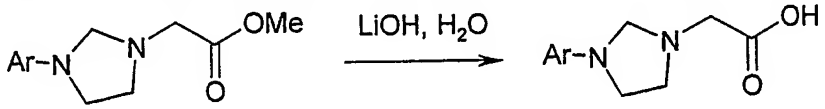
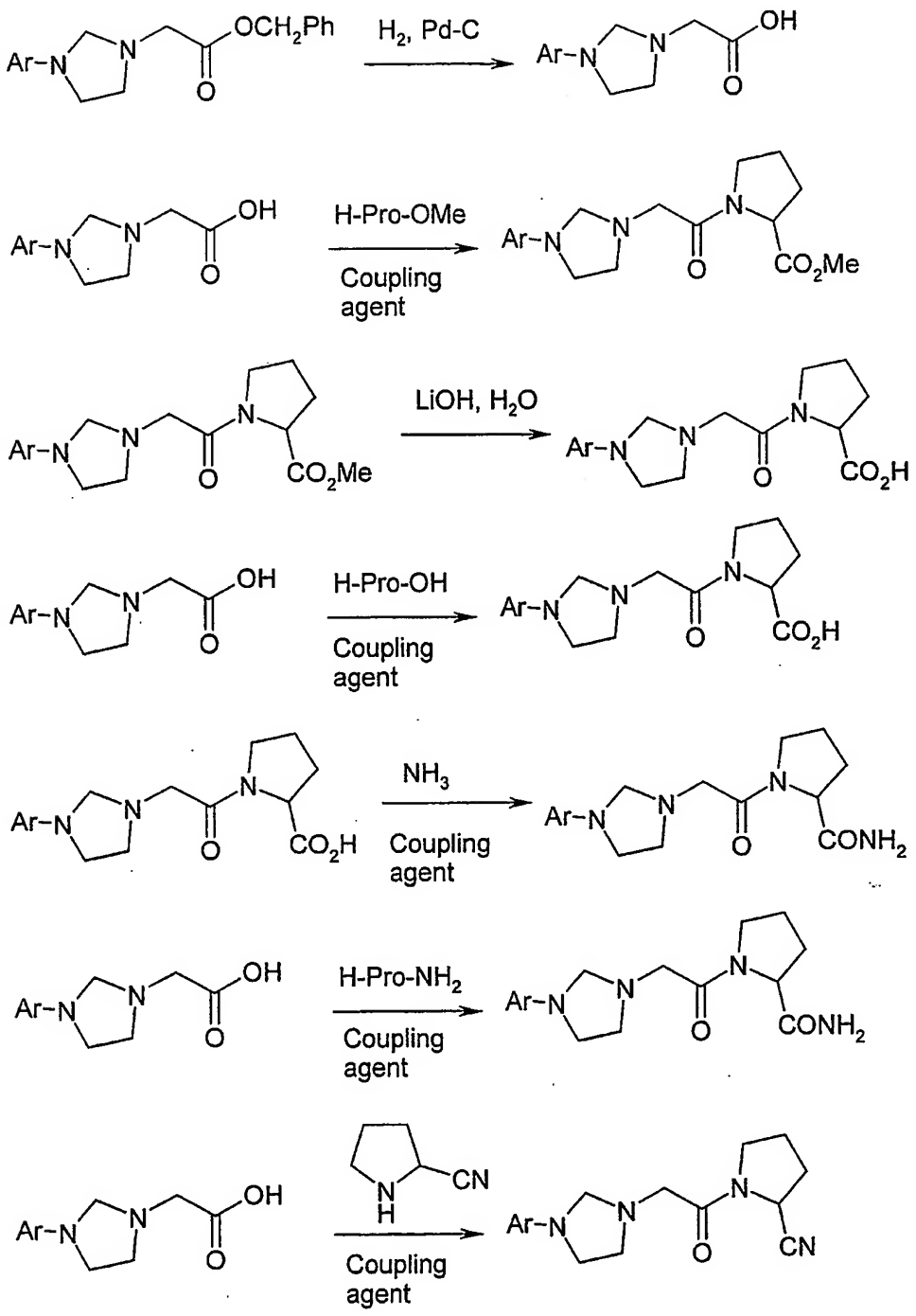
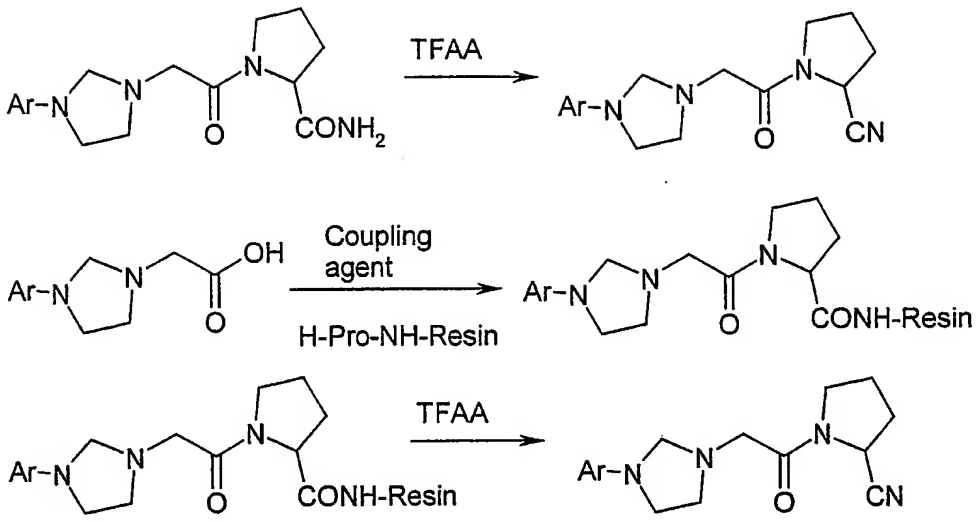
The transformation of compounds according to general formula **1** into these therapeutic agents requires the following processes, which may be performed in any order. (For the sake of clarity these processes are illustrated for the case where R^1 and R^2 are both H, but the methods are valid for other embodiments of these two groups.)

i. Conversion of the group Y into the cyanopyrrolidine moiety of **4**, if Y in **1** is other than 2-cyanopyrrolidine. This conversion can be achieved in one or more steps using well known chemistry. Examples of these steps are illustrated below.

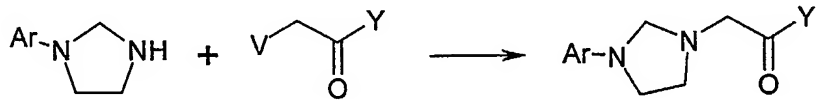



Ar–N
OCH2Ph
H2, Pd-C
OH
H-Pro-OMe
Coupling agent
CO2Me
LiOH, H2O
CO2H
H-Pro-OH
NH3
CONH2
H-Pro-NH2
CN



ii. Liberation of the ethylenediamine functionality from the imidazolidine ring. This may generally be achieved by treatment with aqueous acid, with anhydrous acid in the presence of an aldehyde or ketone scavenger or by treatment with malonic acid and pyridine according to the method of Almeida *et al* (J. Chem. Soc. Perkin Trans. I, *1988*, 1905).

Compounds according to general formula **1** can be prepared by the reaction of an imidazolidine according to general formula **5** with an acetic acid derivative according to general formula **6**, and this reaction is a third aspect of the present invention.

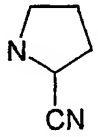


5 **6** **1**

In this reaction scheme Ar is an aryl group selected from optionally substituted phenyl and optionally substituted heteroaryl groups. The optional substituents are selected from alkyl groups, acyl groups, OH, O-alkyl, O-acyl, NH_2, NH-alkyl, $N(alkyl)_2$, NH-acyl, N(alkyl)-acyl, $N(acyl)_2$, F, Cl, Br, I, CF_3, NO_2, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and

CN. The aryl group may have up to three such substituents which may be the same or different. In a preferred embodiment, the group Ar is selected from optionally substituted phenyl and optionally substituted pyridyl. More preferably, it is optionally substituted pyridyl. More preferably still, it is optionally substituted 2-pyridyl. Yet more preferably it is 5-monosubstituted 2-pyridyl. Most preferably it is 5-cyano-2-pyridyl.

The group Y is selected from OH, O-alkyl, O-aralkyl, 2-cyano-1-pyrrolidyl (**2**) and a group according to general formula **3**.



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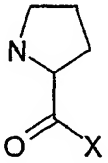


3

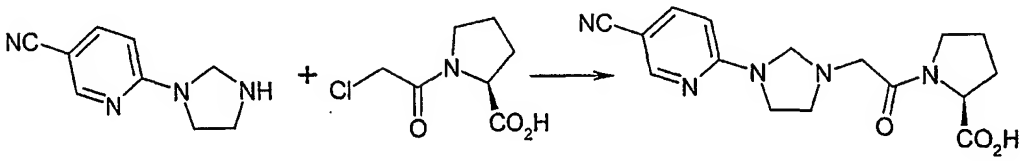
The group X is selected from OH, O-alkyl, O-aralkyl, O-resin, NH_2, NH-alkyl, NH-aralkyl, and NH-resin.

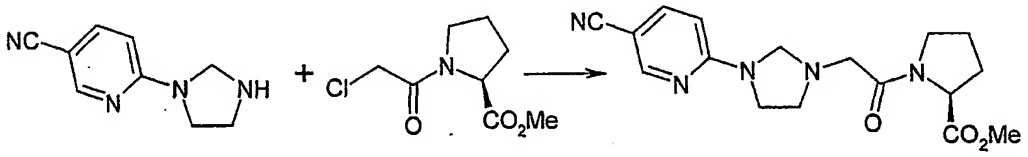
In a preferred embodiment, the group Y is selected from OH, O-alkyl and O-aralkyl. In another preferred embodiment Y is 2-cyano-1-pyrrolidyl, and more preferably it is (2*S*)-2-cyano-1-pyrrolidyl. In another preferred embodiment Y is a group according to general formula **3**. More preferably, Y is a group according to general formula **3** and X is selected from OH, O-alkyl, O-aralkyl, NH_2, NH-alkyl and NH-aralkyl. In another more preferred embodiment X is O-resin or NH-resin.

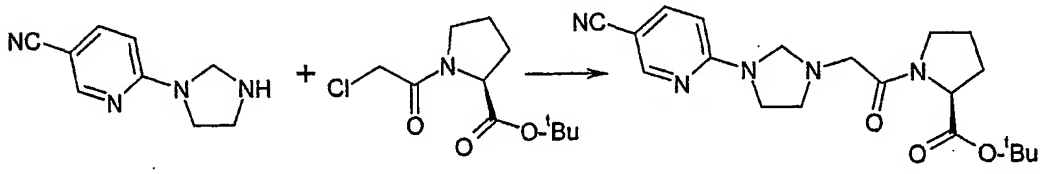
V is a group susceptible to nucleophilic displacement. Suitable groups are Cl, Br, I, alkylsulphonates (alkyl-SO_2-O-), perfluoroalkylsulphonates, optionally substituted benzenesulphonates (Ph(R)-SO_2-O-, where R represents one or more alkyl, perfluoroalkyl or halogen group), acyloxy groups (acyl-O-) and perfluoroacyloxy groups. Preferred groups are Cl, Br, I, methanesulphonate (mesylate), trifluoromethanesulphonate (triflate) and toluenesulphonate (tosylate). More preferably, V is Cl or Br

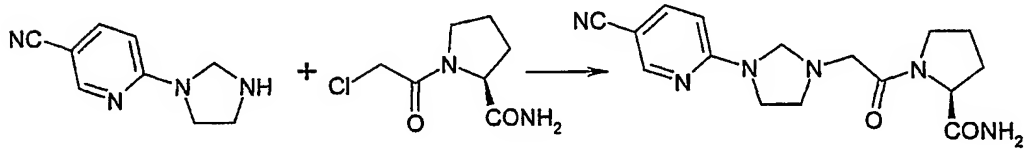
Particularly preferred embodiments of the present invention are those that combine two or more of the above preferred features.

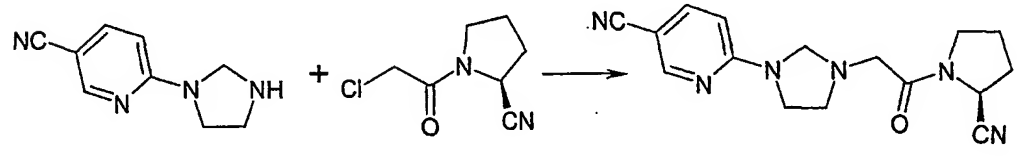
Individually preferred processes of the presented invention include but are not limited to the process shown:

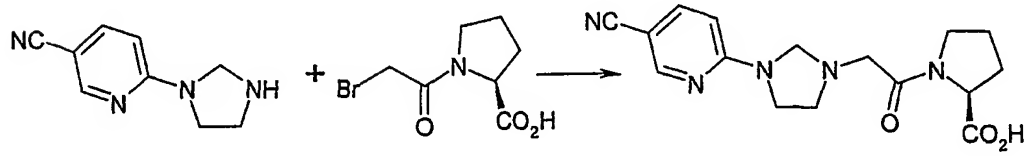


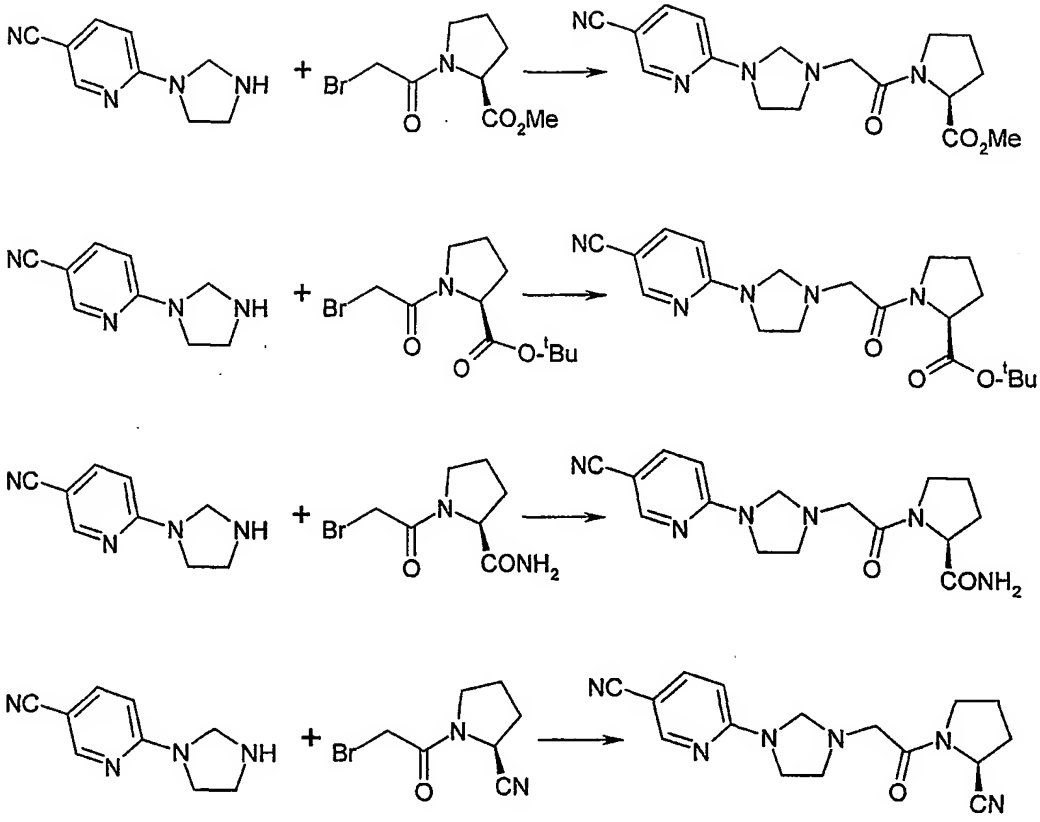




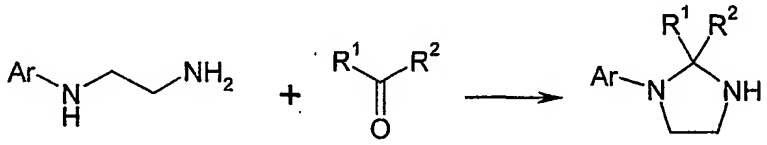








The imidazolidine derivatives according to general formula **5** that serve as starting materials in the process described above can be prepared by the reaction of an ethylenediamine derivative with an aldehyde or ketone.



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The acetic acid derivatives according to general formula **6** that also serve as starting materials in the process are either items of commerce or can be prepared from such items.

Compounds according to general formula **5** in which Ar is an optionally substituted heteroaryl group are themselves novel. Accordingly, in a fourth aspect the present invention comprises compounds according to general formula **5** in which Ar is an optionally

substituted heteroaryl group. The optional substituents are selected from alkyl groups, acyl groups, OH, O-alkyl, O-acyl, NH_2, NH-alkyl, $N(alkyl)_2$, NH-acyl, N(alkyl)-acyl, $N(acyl)_2$, F, Cl, Br, I, CF_3, NO_2, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN. The heteroaryl group may have up to three such substituents which may be the same or different.

In a preferred embodiment Ar is an optionally substituted pyridyl group. More preferably it is a 5-monosubstituted 2-pyridyl group. A particularly preferred embodiment is the compound 1-(5-cyano-2-pyridyl)imidazolidine.

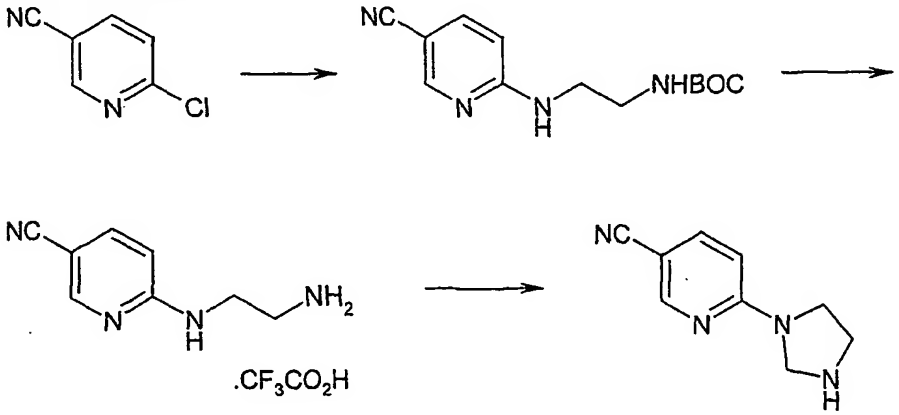
The reaction of an imidazolidine derivative according to general formula **5** with an acetic acid derivative **6** is generally more selective (i.e. it gives fewer side products) and higher yielding than the alkylation of the corresponding ethylenediamine derivative. Accordingly, compounds according to general formula **1** can be readily prepared and easily purified on a commercial scale. Since compounds according to general formula **1** can be transformed into the ethylenediamine derivatives of WO98/19998 or analogues thereof, their use represents a significant improvement in the preparation of these ethylenediamine derivatives.

The present invention is further illustrated in the following non-limiting Examples.

EXAMPLES

Example 1

1-(5-Cyano-2-pyridyl)imidazolidine



1A *tert*-Butyl (2-(5-cyano-2-pyridylamino)ethyl)carbamate

A solution of 6-chloronicotinonitrile (21.7g, 160mmol), potassium hydrogen carbonate (17.6g, 176mmol) and *tert*-butyl (2-aminoethyl)carbamate (25.8g, 160mmol) in DMF (80ml) was heated to 90°C under N_2 for 2.5h. The mixture was cooled, added to saturated $NaHCO_3$ solution and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated until the product started to precipitate. Further product was precipitated by adding petroleum ether. The combined precipitates were collected and washed with cold EtOAc to afford *tert*-butyl (2-(5-cyano-2-pyridylamino)ethyl)carbamate (27.2g, 65%) as a white solid.

^{1}H NMR ($CDCl_3$, 270MHz): δ 1.41 (9H, s), 3.30-3.42 (2H, m), 3.44-3.56 (2H, m), 4.92 (1H, br s), 5.72 (1H, br s), 6.39 (1H, dd, J=8.9, 0.7Hz), 7.51 (1H, dd, 8.9, 2.2Hz), 8.30-8.36 (1H, m) ppm.

1B 6-(2-Aminoethylamino)nicotinonitrile trifluoroacetate

Trifluoroacetic acid (125ml) was added to an ice-cold stirred suspension of *tert*-butyl (2-(5-cyano-2-pyridylamino)ethyl)carbamate (32.0g, 120mmol) in CH_2Cl_2 (125ml) to give a clear solution. After gas evolution had ceased the cooling bath was removed. After 1.5h the mixture was concentrated and azeotroped with toluene 3 times to afford 6-(2-aminoethylamino)nicotinonitrile trifluoroacetate. The yield was assumed to be quantitative and the material was used directly in the next step.

1C 1-(5-Cyano-2-pyridyl)imidazolidine

6-(2-Aminoethylamino)nicotinonitrile trifluoroacetate (120mmol) was dissolved in water (1300ml). Aqueous 37% formaldehyde solution (15.5g, 12.5ml, 168mmol) was added and the mixture was stirred for 3 days. The mixture was concentrated then azeotroped with toluene twice and with petroleum ether once. The residue was taken up in Et_2O/EtOH (50:50, 200ml) and scratched to initiate crystallisation. The mixture was cooled in an ice/water bath for 4h and filtered to afford 1-(5-cyano-2-pyridyl)imidazolidine trifluoroacetate (11.4g, 33%) as a pale yellow crystalline solid.

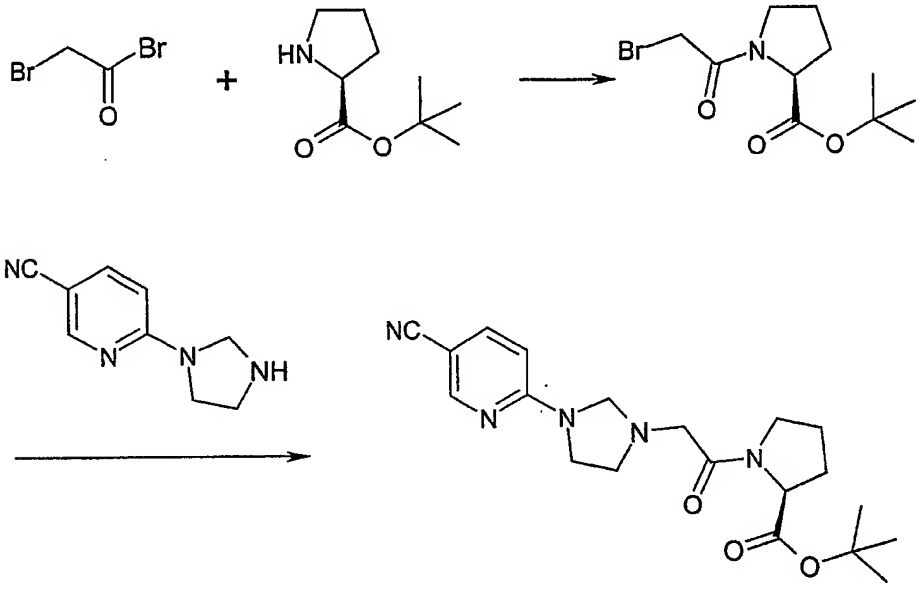
^{1}H NMR (d_6 DMSO, 270MHz): δ 3.58-3.78 (4H, m), 4.75 (2H, s), 6.78 (1H, d, J=8.9Hz), 8.01 (1H, dd, J=2.2, 8.9Hz), 8.58 (1H, d, J=2.2Hz) ppm.

This was dissolved in water and saturated $NaHCO_3$ solution was added until the solution was basic. The mixture was extracted with CH_2Cl_2 four times and the combined organic extracts were dried over Na_2SO_4 and concentrated to afford 1-(5-cyano-2-pyridyl)-imidazolidine free base (6.7g, 32%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 270MHz): δ 3.26-3.48 (4H, m), 4.46 (2H, s), 6.28 (1H, d, J=8.7Hz), 7.57 (1H, dd, J=2.2, 8.7Hz), 8.37 (1H, d, J=2.2Hz) ppm.

Example 2

***N*-(2-(3'-(5''-cyano-2''-pyridyl)imidazolidine)acetyl)-L-proline *tert*-butyl ester**



2A. *N*-Bromoacetyl-L-proline *tert*-butyl ester

A solution of L-proline *tert*-butyl ester (5.0g, 29mmol), DMAP (15mg) and triethylamine (3.5g, 4.9ml, 35mmol) in CH_2Cl_2 (100ml) was added dropwise to an ice-cold solution of bromoacetyl bromide (6.4g, 2.8ml, 32mmol) in CH_2Cl_2 (75ml). After 90min, EtOAc (800ml) was added and the mixture was filtered and concentrated to give *N*-bromoacetyl-L-proline *tert*-butyl ester. The yield was assumed to be quantitative and the material was used directly in the next step.

^{1}H NMR ($CDCl_3$, 270MHz): δ 1.42 (9H, s), 1.80-2.28 (4H, m), 3.48-3.86 (2H, m), 3.71 and 3.79 (total 2H in the ratio 1:3, each s), 4.08 and 4.33 (total 1H in the ratio 3:1, dd, J=7.2, 14.4Hz and dd, J=3.7, 8.3Hz) ppm.

2B. *N*-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-proline *tert*-butyl ester

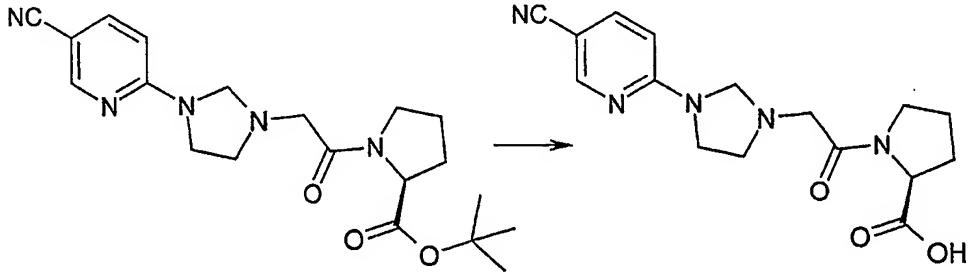
A solution of *N*-bromoacetyl-L-proline *tert*-butyl ester (2.0g, 6.9mmol) in THF (5ml) was added to an ice-cold solution of 1-(5-cyano-2-pyridyl)imidazolidine (1.0g, 5.7mmol) and triethylamine (1.1ml, 0.81g, 8.0mmol) in THF (10ml). The resulting cloudy mixture was allowed to warm to room temperature and stirred for 24h. The mixture was added to dilute K_2CO_3 solution and extracted with CH_2Cl_2 three times. The combined organic extracts were dried over Na_2SO_4 and concentrated. Chromatography (2.5% MeOH/97.5% CH_2Cl_2) afforded *N*-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-proline *tert*-butyl ester (0.77g, 35%) as a golden oil.

^{1}H NMR ($CDCl_3$, 270MHz): δ 1.44 (9H, s), 1.80-2.24 (4H, m), 2.90-3.72 (8H, m), 4.24-4.46 (3H, m), 6.27 (1H, d, J=8.9Hz), 7.57 (1H, dd, J=8.9,2.0Hz), 8.37 (1H, d, J=2.0Hz, 6"CH) ppm.

MS (ESI) *m/z* 386.2 (MH^+)

Example 3

***N*-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-proline**



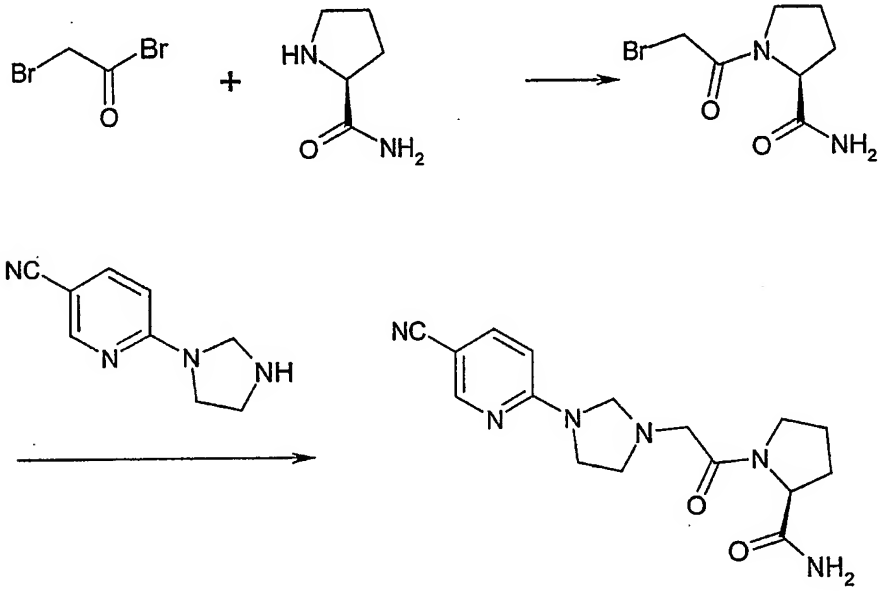
A solution of *N*-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-proline *tert*-butyl ester (109mg, 0.28mmol) in CH_2Cl_2 (0.5ml) and trifluoroacetic acid (1ml) was stirred for 2.5h. The mixture was reduced to dryness to afford *N*-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-proline trifluoroacetate salt as a yellow gum. The yield was assumed to be quantitative.

^{1}H NMR (d_6 DMSO, 270MHz): δ 1.82-2.02 (3H, m) and 2.08-2.26 (1H, m), 3.30-3.96 (8H, m), 4.20-4.66 (3H, m), 6.79 (1H, d, J=8.9Hz), 8.03 (1H, dd, J=2.2, 8.9Hz), 8.59 (1H, d, J=2.2Hz) ppm.

MS (ESI) *m/z* 330.2 (MH^+).

Example 4

***N*-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-prolineamide**



4A *N*-Bromoacetyl-L-prolineamide

A solution of L-prolinamide (9.9g, 87mmol), DMAP (15mg) and triethylamine (10.5g, 14.5ml, 104mmol) in CH_2Cl_2 (125ml) was added dropwise to an ice-cold solution of bromoacetyl bromide (19.3g, 8.3ml, 96mmol) in CH_2Cl_2 (75ml) over 1h. After a further 2h, EtOAc (1500ml) was added and the mixture was filtered and concentrated to give *N*-bromoacetyl-L-prolineamide (20.4g, 100%).

^{1}H NMR ($CDCl_3$, 270MHz): δ 1.88-2.42 (4H, m), 3.50-3.74 (2H, m), 3.85 (2H, s), 4.44-4.60 (1H, m), 5.56-5.88 (1H, br s), 6.80 (1H, br s) ppm.

4B. *N*-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-prolineamide

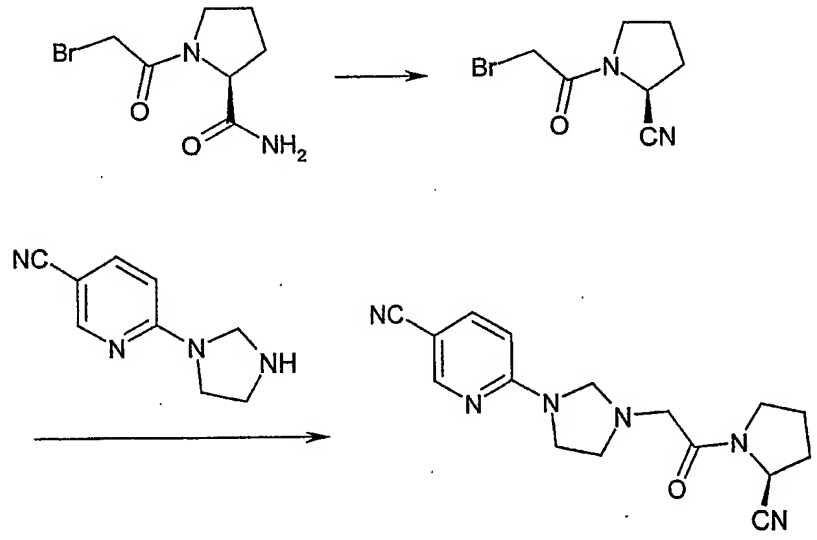
A solution of *N*-bromoacetyl-L-prolineamide (0.79g, 3.34mmol) in THF (5ml) was added to an ice-cold solution of 1-(5-cyano-2-pyridyl)imidazolidine (0.49g, 2.8mmol) and triethylamine (0.54ml, 0.40g, 3.9mmol) in THF (10ml). The resulting cloudy mixture was allowed to warm to room temperature and stirred for 4 days. The mixture was added to dilute K_2CO_3 solution and extracted with CH_2Cl_2 four times. The combined organic extracts were dried over Na_2SO_4 and concentrated. Chromatography (10% MeOH/90% CH_2Cl_2) afforded *N*-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-prolineamide (0.14g, 15%) as a white foam.

^{1}H NMR (d_6 DMSO, 270MHz): δ1.78-2.30 (3H, m) and 2.32-2.46 (1H, m), 3.08-3.28 (2H, m), 3.32-3.72 (6H, m), 4.26-4.50 (2H, m), 4.59 (1H, dd, J=2.2, 8.2Hz), 5.47 (1H, br s), 6.29 (1H, d, J=8.9Hz), 6.92 (1H, br s), 7.59 (1H, dd, J=1.7, 8.9Hz), 8.37 (1H, d, J=1.7Hz) ppm.

MS (ESI) *m/z* 329.2 (MH^+).

Example 5

(2*S*)-1-(2′-(3″-(5‴-cyano-2‴-pyridyl)imidazolidine)acetyl)pyrrolidine-2-carbonitrile



5A (2*S*)-1-(Bromoacetyl)pyrrolidine-2-carbonitrile

N-Bromoacetyl-L-prolineamine (20.4g, 87mmol) was dissolved in CH_2Cl_2 (120ml) and cooled in an ice/water bath. The cold solution was added to ice-cold trifluoroacetic

anhydride (24.6ml, 36.5g, 174mmol) under N_2 over 15min. After 2h the mixture was added cautiously to saturated $NaHCO_3$ while cooling in an ice/water bath. The phases was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with water, dried over Na_2SO_4 and concentrated. Chromatography (75% EtOAC/25% petroleum ether) afforded (2*S*)-1-(bromoacetyl)pyrrolidine-2-carbonitrile (3.94g, 21%) as an orange oil.

^{1}H NMR ($CDCl_3$, 270MHz): δ 2.00-2.50 (4H, m), 3.44-4.02 (2H, m), 3.81 (2H, s), 4.68-4.80 and 4.82-4.90 (total 1H, each m) ppm.

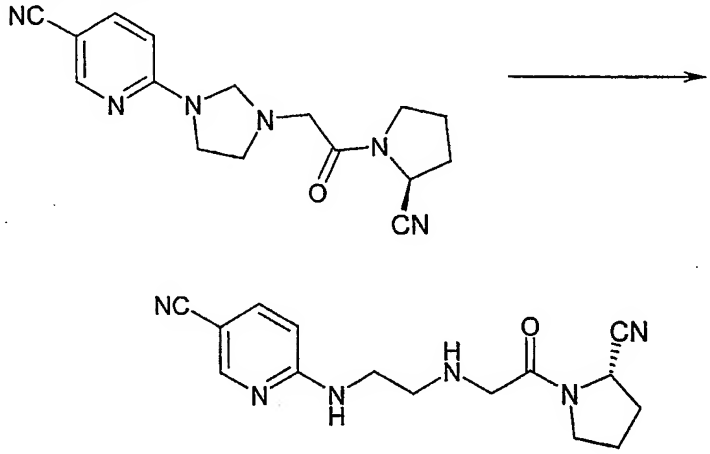
5B (2*S*)-1-(2'-(3''-(5'''-Cyano-2'''-pyridyl)imidazolidine)acetyl)pyrrolidine-2-carbonitrile
A solution of (2*S*)-1-(bromoacetyl)pyrrolidine-2-carbonitrile (3.94g, 18.1mmol) in THF (20ml) was added to an ice-cold solution of 1-(5-cyano-2-pyridyl)imidazolidine (3.16g, 18.1mmol) and triethylamine (2.8ml, 2.0g, 20mmol) in THF (20ml) over 3min. The resulting cloudy mixture was allowed to warm to room temperature and stirred for 6h. The mixture was added to dilute $NaHCO_3$ solution and extracted with CH_2Cl_2 four times. The combined organic extracts were dried over Na_2SO_4 and concentrated. Chromatography (2.5% MeOH/97.5% CH_2Cl_2) afforded (2*S*)-1-(2'-(3''-(5'''-cyano-2'''-pyridyl)imidazolidine)-acetyl)pyrrolidine-2-carbonitrile (3.4g, 61%) as a white foam.

^{1}H NMR ($CDCl_3$, 270MHz): δ2.04-2.42 (4H, m), 3.18 (2H, t, J=6.7Hz), 3.34-3.76 (6H) 4.26-4.42 (2H) (each m, 5CH_2, 2"CH_2, 4"CH_2 and 2'CH_2), 4.74-4.80 and 4.95-5.04 (total 1H in the ratio 3:1, each m), 6.30 (1H, d, J=8.9Hz), 7.60 (1H, dd, J=2.0, 8.9Hz), 8.38 (1H, d, J=2.0Hz).

MS (ESI) *m/z* 311.0 (MH^+).

Example 6

(2*S*)-1-(2'-(5''-cyano-2''-pyridylamino)ethylamino)acetyl)pyrrolidine-2-carbonitrile



A solution of (2*S*)-1-(2'-(3''-(5'''-cyano-2'''-pyridyl)imidazolidine)acetyl)pyrrolidine-2-carbonitrile (3.15g, 10.2mmol) in 10% trifluoroacetic acid (250ml) was stirred for 24h. The mixture was cooled in an ice/water bath and potassium carbonate was added cautiously until saturated, then extracted with CH_2Cl_2 seven times. The combined extracts were dried over Na_2SO_4 and concentrated. Chromatography (10% MeOH/90% CH_2Cl_2) afforded (2*S*)-1-(2'-(5''-cyano-2''-pyridylamino)ethylamino)acetyl)pyrrolidine-2-carbonitrile (1.53g, 50%) as a colourless gum.

^{1}H NMR at 25°C was consistent with the presence of two rotameric isomers in a ratio of ~85:15.

^{1}H NMR (d_6 DMSO, 270MHz): δ 1.84-2.30 (4H, m), 2.71 (2H, t, J=6.2Hz), 3.22-3.48 (5H, m), 3.50-3.66 (1H, m), 4.73 and 5.13 (1H, ratio ~85:15, dd, J=4.7, 6.4Hz and dd, J=2.5, 6.7Hz), 6.56 (1H, d, J=8.9Hz), 7.50-7.72 (2H, m), 8.36 (1H, d, J=2.0Hz) ppm.

At higher temperatures the NMR signals of the two compounds appeared to coalesce as is typical of rotameric isomers.

^{1}H NMR (d_6 DMSO, 270MHz): δ 1.98-2.30 (4H, m), 2.77 (2H, t, J=6.2Hz), 3.30-3.62 (6H, m), 4.62-4.88 (1H, m), 6.57 (1H, d, J=8.9Hz), 7.26 (1H, br s), 7.61 (1H, dd, J=2.2, 8.9Hz), 8.33 (1H, d, J=2.2Hz) ppm.

4N HCl/dioxan (1.3ml, 5.1mmol) was added to a solution of (2*S*)-1-(2′-(5″-cyano-2″-pyridylamino)ethylamino)acetyl)pyrrolidine-2-carbonitrile (1.53g, 5.13mmol) to afford a white precipitate. The solid was filtered, washed and triturated with Et_2O and dried *in vacuo* over P_2O_5 to yield (2*S*)-1-(2′-(5″-cyano-2″-pyridylamino)ethylamino)acetyl)-pyrrolidine-2-carbonitrile hydrochloride salt (1.40g, 82%) as a white powder. An analytical sample was recystallised from MeOH, m. pt. = 158-163°C.

^{1}H NMR (d_6 DMSO, 270MHz): δ 1.88-2.30 (4H, m), 3.13 (2H, s), 3.32-3.50 (1H, m), 3.52-3.98 (4H, m), 4.00-4.22 (1H, m), 4.84 (1H, t, J=5.6Hz), 6.64 (1H, d, J=8.9Hz), 7.76 (1H, dd, J=8.9, 2.1Hz), 8.00 (1H, br s), 8.43 (1H, d, J=2.1Hz), 9.25 (2H, br s) ppm.

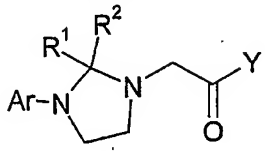
^{13}C NMR (D_2O, 68MHz): δ 24.7, 29.6, 38.2, 46.3, 47.0, 47.1, 48.2, 97.3, 111.5, 117.9, 118.7, 141.6, 149.5, 156.8, 165.0 ppm.

MS (ESI) *m/z* 299.1 (MH^+).

As illustrated in the foregoing Examples, the use of imidazolidine derivatives provides a simple and convenient route to *N*-(aminoethyl)glycine derivatives such as NVP-DPP728. In particular, the improved selectivity in the alkylation step reduces the need for lengthy purification procedures, so improving the overall efficiency of the process.

CLAIMS

1 A compound according to general formula **1**, or a salt thereof



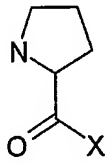
1

wherein:

Ar is selected from optionally substituted phenyl and optionally substituted heteroaryl;

R^1 and R^2 are independently selected from H and alkyl;

Y is selected from OH, O-alkyl, O-aralkyl, 2-cyano1-pyrrolidyl and a group according to general formula **3**



3

and X is selected from OH, O-alkyl, O-aralkyl, O-resin, NH_2, NH-alkyl, NH-aralkyl and NH-resin.

2 A compound according to Claim 1 wherein R^1 and R^2 are independently selected from H, methyl and ethyl.

3 A compound according to Claim 1 or 2 wherein R^1 and R^2 are independently selected from H and methyl.

4 A compound according to Claim 1 or 2 wherein R^1 and R^2 are both H.

5 A compound according to Claim 1 or 2 wherein R^1 and R^2 are both methyl.

6 A compound according to any of Claims 1 to 5 wherein Ar is selected from optionally substituted phenyl and optionally substituted pyridyl.

7 A compound according to any of Claims 1 to 6 wherein Ar is optionally substituted pyridyl.

8 A compound according to any of Claims 1 to 7 wherein Ar is optionally substituted 2-pyridyl.

9 A compound according to any of Claims 1 to 8 wherein Ar is 5-monosubstituted-2-pyridyl.

10 A compound according to any of Claims 1 to 9 wherein Ar is 5-cyano-2-pyridyl.

11 A compound according to any of Claims 1 to 10 wherein Y is selected from OH, O-alkyl and O-aralkyl.

12 A compound according to any of Claims 1 to 10 wherein Y is 2-cyano-1-pyrrolidyl.

13 A compound according to any of Claims 1 to 10 wherein Y is a group according to general formula **3**.

14 A compound according to any of Claims 1 to 10 or Claim 13 wherein Y is a group according to general formula **3** and X is selected from OH, O-alkyl, O-aralkyl, NH_2, NH-alkyl and NH-aralkyl.

15 A compound according to any of Claims 1 to 10 or Claim 13 wherein Y is a group according to general formula **3** and X is selected from O-resin and NH-resin.

16 A compound selected from

N-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-proline;

N-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-proline methyl ester;

N-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-proline benzyl ester;

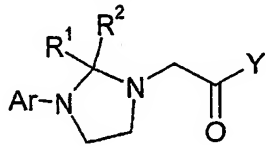
N-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-proline *tert*-butyl ester;

N-(2-(3′-(5″-cyano-2″-pyridyl)imidazolidine)acetyl)-L-prolineamide; and

(2*S*)-1-(2′-(3″-(5‴-cyano-2‴-pyridyl)imidazolidine)acetyl)pyrrolidine-2-carbonitrile,

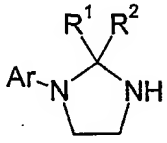
or a salt thereof.

17 A process for the manufacture of a compound according to general formula **1**

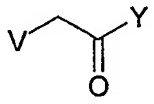


1

which comprises the reaction of an imidazolidine according to general formula **5** and an acetic acid derivative according to general formula **6**



5



6

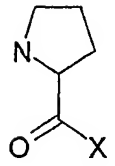
wherein:

Ar is selected from optionally substituted phenyl and optionally substituted heteroaryl;

R^1 and R^2 are independently selected from H and alkyl;

V is selected from Br, Cl, I, alkylsulphonate, perfluoroalkylsulphonate, optionally substituted benzenesulphonate, acyloxy and perfluoroacyloxy groups;

Y is selected from OH, O-alkyl, O-aralkyl, 2-cyano1-pyrrolidyl and a group according to general formula **3**



3

and X is selected from OH, O-alkyl, O-aralkyl, O-resin, NH_2, NH-alkyl, NH-aralkyl and NH-resin

18 A process according to Claim 17 wherein V is selected from Cl, Br, I, methanesulphonate, trifluoromethanesulphonate and toluenesulphonate.

19 A process according to Claim 17 or 18 wherein V is selected from Cl and Br.

20 A process according to any of Claims 17 to 19 wherein Y is selected from OH, O-alkyl and O-aralkyl.

21 A process according to any of Claims 17 to 19 wherein Y is 2-cyano-1-pyrrolidyl.

22 A process according to Claim 21 wherein Y is (2*S*)-2-cyano-1-pyrrolidyl.

23 A process according to any of Claims 17 to 19 wherein Y is a group according to general formula **3**.

24 A process according to any of Claims 17 to 19 and Claim 23 wherein Y is a group according to general formula **3** and X is selected from OH, O-alkyl, O-aralkyl, NH_2, NH-alkyl and NH-aralkyl.

25 A process according to any of Claims 17 to 19 and Claim 23 wherein Y is a group according to general formula **3** and X is selected from O-resin and NH-resin.

26 A process according to any of Claims 17 to 19 which comprises the reaction of 6-(1-imidazolidinyl)nicotinonitrile with an alkylating agent selected from

N-(chloroacetyl)proline;

N-(chloroacetyl)proline methyl ester;

N-(chloroacetyl)proline *tert*-butyl ester;

N-(chloroacetyl)prolineamide;

(2S)-1-chloroacetylpyrrolidine-2-carbonitrile;

N-(bromoacetyl)proline;

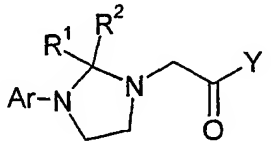
N-(bromoacetyl)proline methyl ester;

N-(bromoacetyl)proline *tert*-butyl ester;

N-(bromoacetyl)prolineamide; and

(2S)-1-bromoacetylpyrrolidine-2-carbonitrile.

27 The use of a compound according to general formula **1**



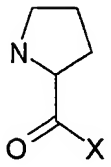
1

wherein:

Ar is selected from optionally substituted phenyl and optionally substituted heteroaryl;

R^1 and R^2 are independently selected from H and alkyl;

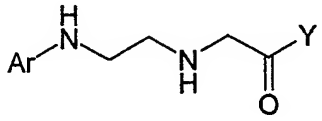
Y is selected from OH, O-alkyl, O-aralkyl, 2-cyano-1-pyrrolidyl and a group according to general formula **3**



3

and X is selected from OH, O-alkyl, O-aralkyl, O-resin, NH_2, NH-alkyl, NH-aralkyl and NH-resin, which use is as a component in the manufacture of a pharmaceutical agent.

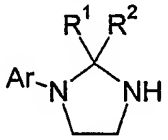
28 A use according to Claim 27 wherein the pharmaceutical agent is a compound according to general formula **4**



4

wherein Ar and Y are as defined in Claim 27.

29 A compound according to general formula **5**, or a salt thereof



5

wherein Ar is optionally substituted phenyl or optionally substituted heteroaryl; and R^1 and R^2 are independently selected from H and alkyl.

30 A compound according to claim 29, or salt thereof, wherein the phenyl or heteroaryl group substituent(s) is selected from alkyl groups, acyl groups, OH, O-alkyl, O-acyl, NH_2, NH-alkyl, $N(alkyl)_2$, NH-acyl, N(alkyl)-acyl, $N(acyl)_2$, F, Cl, Br, I, CF_3, NO_2, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN.

31 A compound according to claim 29 or claim 30 with the proviso that when R^1 and R^2 are both H, Ar is not 4-methoxyphenyl.

32 A compound according to Claim 29, 30 or 31, or salt thereof, wherein R^1 and R^2 are both H.

33 A compound according to any of claims 29 to 32, or salt thereof , wherein Ar is optionally substituted pyridyl.

34 A compound according to any of claims 29 to 33, or salt thereof , wherein Ar is a 5-monosubstituted-2-pyridyl group.

35 1-(5-Cyano-2-pyridyl)imidazolidine, or a salt thereof.

36 A process for the manufacture of (2S)-1-(2-(5-cyanopyridyl-2-amino)ethylamino-acetyl)pyrrolidine-2-carbonitrile (NVP-DPP728) that comprises the steps of

(i) reacting 1-(5-cyano-2-pyridyl)imidazolidine with an N-(haloacetyl)-proline, or ester or amide thereof, or with an N-(haloacetyl)pyrrolidine-2-carbonitrile; and

(ii) optionally modifying the carboxylic acid, ester or amide functionality so as to provide a carbonitrile functional group; and

(iii) treating the product so obtained with an acid so as to open the imidazolidine ring and give an ethylenediamine derivative.